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A Newer series of 1, 3-Thiazole Derivatives: Synthesis, Structure Elucidation and Biological Screening for Bacterial and Fungal Species

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Abstracts: *Antibiotics are generally used to treat bacterial infections. The toxicity to humans and other animals from antibiotics is generally considered to be low. An antifungal drug is medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcalmeningitis, and others. Newer thiazole derivatives are designed and synthesis as per specific methods. The entire synthesized compound was characterized with Mass, NMR and IR spectroscopy. After synthesis the compounds were evaluated for their antibacterial activity against Staphylococcus aureus and Bacillus substillis as Gram positive bacteria and Escherichia coli as Gram negative bacteria. They were also evaluated for their antifungal potential against Candida tropicalis as yeast and Aspergillus niger as mould. After pharmacological screening we got some thiazole derivatives which are better effective against various microbial and fungal species.*

Key words: *Anti Microbial, Anti Fungal, Thiazole, Amoxicillin, Streptomycin, Fluconazole*

1. INTRODUCTIONS:

Antibiotics are generally used to treat bacterial infections. The toxicity to humans and other animals from antibiotics is generally considered to be low. However, prolonged use of certain antibiotics can decrease the number of gut flora, which can have a negative impact on health. Some recommend that during or after prolonged antibiotic use, that one should consume probiotics and eat reasonably to replace destroyed gut flora. An antifungal drug is medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcalmeningitis, and others. There are various examples of different heterocyclic compounds which act as antibiotics and antifungal. Thiazole containing derivatives gives remarkable activity against various microbial and fungal species. Thiazole is a five member heterocyclic compound containing two hetero atoms nitrogen and sulpher. Newer thiazole derivatives are designed and synthesis as per specific methods. The entire synthesized compound was characterized with Mass, NMR and IR spectroscopy. After synthesis the compounds were evaluated for their antibacterial activity against Staphylococcus aureus and Bacillus substillis as Gram positive bacteria and Escherichia coli as Gram negative bacteria. They were also evaluated for their antifungal potential against Candida tropicalis as yeast and Aspergillus niger as mould. Agar well diffusion method was widely used for determination of the preliminary antibacterial and antifungal activity. Amoxicillin, Streptomycin as antibacterial, Fluconazole as antifungal were used as a standard drugs.

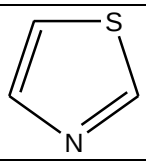
Structure of Thiazole	
IUPAC name	1,3-Thiazole
Molecular Formula	C_3H_3NS
Molecular weight	85 gm/mol
Boiling Point	388K
Melting point	294K
log P	0.77

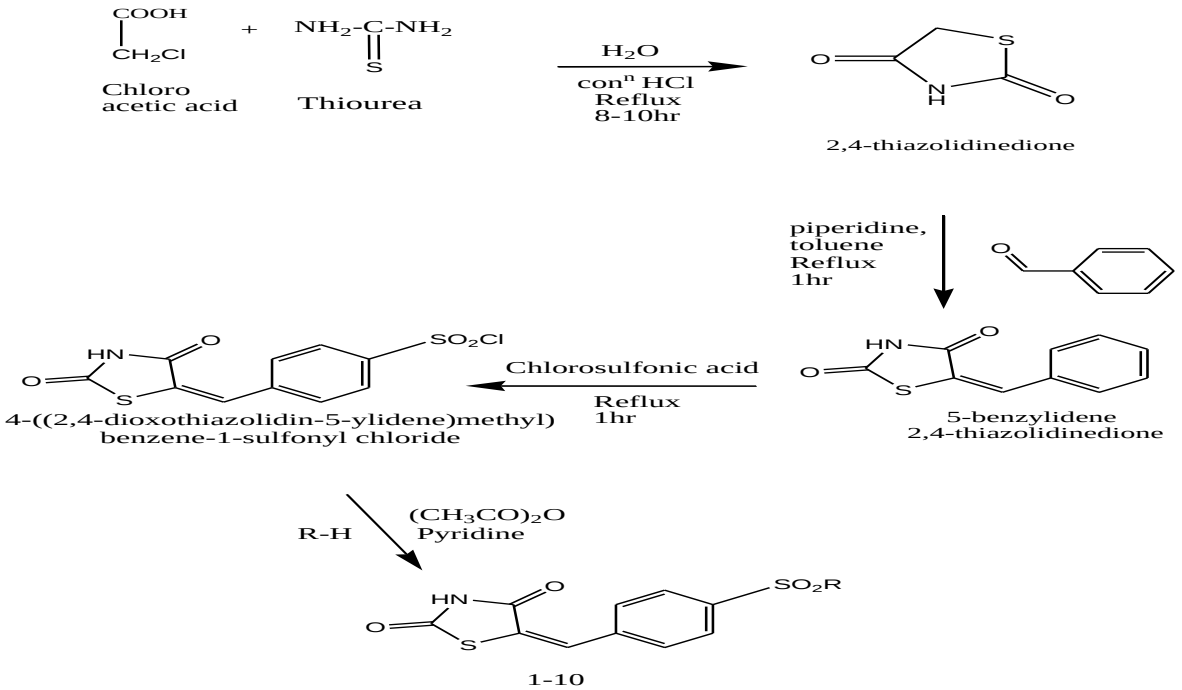
Table: 1 General information of Thiazole derivatives

2. EXPERIMENTAL WORK:

2.1. Synthesis of Newer compounds:

- Synthesis of 2,4-thiazolidinedione: Solution containing 56.5gm (0.6M) Chloroacetic acid in 60 mL of water and 45.6gm (0.6M) thiourea dissolved in 60 mL of water were placed in 250 mL round-bottomed flask. The mixture was stirred for 15 min, followed by cooling to obtain white precipitates. To the content of the flask 60 mL con. HCl was added slowly from dropping funnel. The mixture was refluxed for 8-10 hr at 100-110oC. On cooling the content of the flask solidified into a cluster of white needles. The product was filtered & washed with water to remove the trace of HCl and dried. The product was recrystallised from ethyl alcohol.
- Synthesis of 5-benzylidene 2,4-thiazolidinedione: Benzaldehyde (20 gm, 0.188 mole), 2,4-thiazolidinedione (22 gm, 0.188 mole) and catalytic amount of piperidine (1 mL) were suspended in dry toluene in 250 mL round-bottomed flask provided with a Dean-Stark apparatus. The mixture was refluxed with stirring. After complete removal of water & when the temperature crossed 110oC, the reaction mixture was stirred for a further 1 hr. On cooling the product precipitated out from toluene. The compound was filtered & washed with cold dry toluene & dry ethanol.
- Synthesis of 4-((2,4-dioxothiazolidin-5-ylidene)methyl)benzene-1-sulfonyl chloride: Benzylidene 2,4-thiazolidinedione (8gm, 0.0388 mole) was placed in a 100 mL round bottom flask equipped with condenser & a dropping funnel. Chlorosulphonic acid (18.08 gm, 0.155 moles) was added at room temperature using dropping funnel. After addition of Chlorosulphonic acid was over the reaction mixture was refluxed for 1 hr on a water bath. The reaction mixture was cooled and poured into a crused ice. The product was filtered and dried. The product was recrystallized from ethanol.
- Synthesis of 4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-phenylbenzenesulfonamide: 4-((2,4-dioxothiazolidin-5-ylidene)methyl)-benzene-1-sulfonyl chloride (0.1 mole) & aniline (0.1 mole) were added to a mixture of 4 mL of dry pyridine & 20 mL of acetic anhydride. The mixture was refluxed for 8 hrs. The completeness of the reaction was checked by the TLC. Then the reaction mixture was poured into 20 mL of ice-water & the solid obtained was filtered & recrystallized from ethanol.
- Synthesis of newer thiazole derivatives: 4-((2,4-dioxothiazolidin-5-ylidene)methyl)-benzene-1-sulfonyl chloride (0.1 mole) & different aniline derivatives/morpholine/L-Proline (0.1 mole) were added to a mixture of 4 mL of dry pyridine & 20 mL of acetic anhydride. The mixture was refluxed for 10 hrs. The completeness of the reaction was checked by the TLC. Then the reaction mixture was poured into 20 mL of ice-water & the solid obtained was filtered & recrystallized from ethanol.

2.2. Synthetic Scheme of Newer compounds:



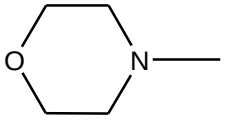
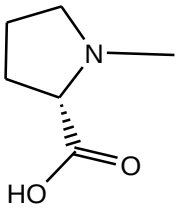
R	Compound	R	Compound
C_6H_5-NH-		4-OHC_6H_5-NH-	
4-$NO_2C_6H_5$-NH-		4-$COOHC_6H_5$-NH-	
2-$NO_2C_6H_5$-NH-		4-$COCH_3C_6H_5$-NH-	
4-FC_6H_5-NH-			
2-$OCH_3C_6H_5$-NH-			0

Table-2 Different derivatives of newer thiazole Compounds

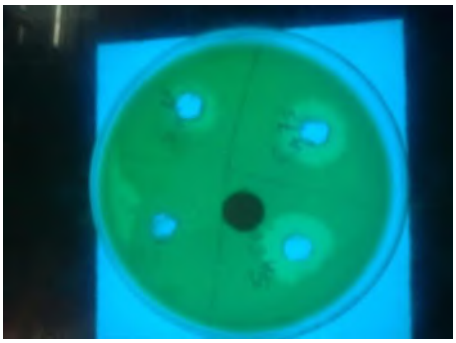
3. SPECTRAL CHARACTERISTICS:

***3*.1. IR Spectra:** The Infrared spectra for the synthesized compounds were recorded using SHIMADZU-FTIR 8400S spectrometer using KBr background. IR spectra of all compounds show two prominent peak of CO at 1760 and 1640 cm-1 which indicates the presence of cyclic ketone. Two bands around 1320 and 1160 cm-1 confirm the presence of SO2 group, while SO2NH group shows prominent peak around 950 cm-1.

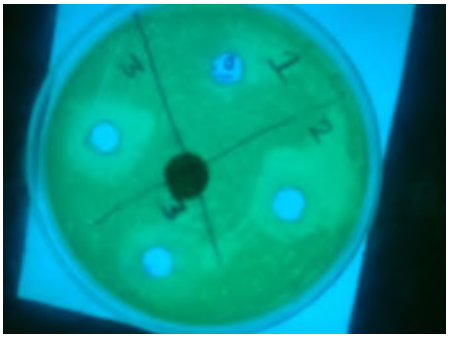
3.2. 1H NMR Spectra: 1H NMR spectra of the synthesized compounds were taken using BRUKER Advance-II 400 MHZ spectrometer using tetramethyl silane as an internal standard. 1H NMR spectra were recorded with DMSO as a solvent & the chemical shift data were expressed as delta values related to TMS. The aryl hydrogen peaks were showed in the range 7.4-8.9 ppm. Secondary amine hydrogen (-NH-CO) showed a single peak around 9.4 ppm.

3.3. Mass Spectra: Mass spectra of the synthesized compounds were taken using 2010EV LCMS SHIMADZU instrument at 70 eV. The mass spectra of these compounds exhibited intense molecular ion peak (M) and one unit less than molecular weight of the compound (M-1)+. Other prominent peaks are assigned to the daughter ions arising through loss of various fragments from the parent molecular ion.

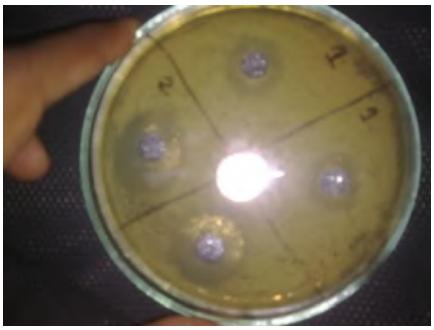
3.4. Biological Evaluation: All the synthesized compounds were evaluated for their antibacterial activity against Staphylococcus aureus and Bacillus substillis as Gram positive bacteria and Escherichia coli as Gram negative bacteria. They were also evaluated for their antifungal potential against Candida tropicalis as yeast and Aspergillus niger as mould. Agar well diffusion method was widely used for determination of the preliminary antibacterial and antifungal activity. Amoxicillin, Streptomycin as antibacterial, Fluconazole as antifungal were used as a standard drugs. The results were recorded for each tested compound as the average diameter of zone of inhibition of bacterial or fungal growth around the discs in mm. regarding the antibacterial activity, most of the tested compounds revealed moderate activity against both the Gram positive and the Gram negative bacteria and also exhibited moderate activity against both yeast and mould.



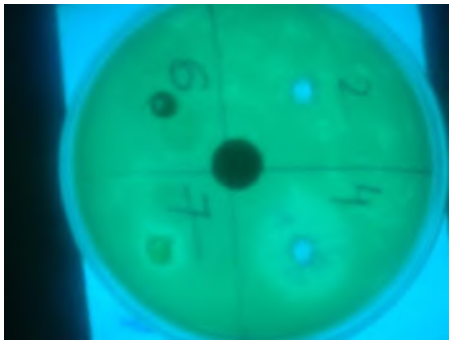
Gram positive(*s.aureus*)



Gram negative (*E.coli.*)



Mould (*A.niger)*



Yeast (*C. tropicalis)*

Compounds (Concentration* mmol)	Antibacterial activity (mm)		
	Gram positive		Gram negative
	S.a.*	B.s*	E.c.*
1	13	12	14
2	15	16	15
3	12	12	12
4	**25**	**19**	**19**
5	**30**	**30**	**25**
6	**26**	**25**	**19**
7	13	15	15
8	09	12	12
9	**25**	**26**	**22**
10	18	21	17
Amoxicillin	26	29	26
Streptomycin	33	31	38
DMSO	---	---	---

Table: 3 The zone of inhibition values (mm) of compounds [1-10]: *E.c. - *Escherichia coli* *B.s -*Bacillus substillis**S.a.- *Staphylococcus aureus* DMSO - No activity *std. drug concentration: 0.1mmol & Test compound concentration: 1mmol

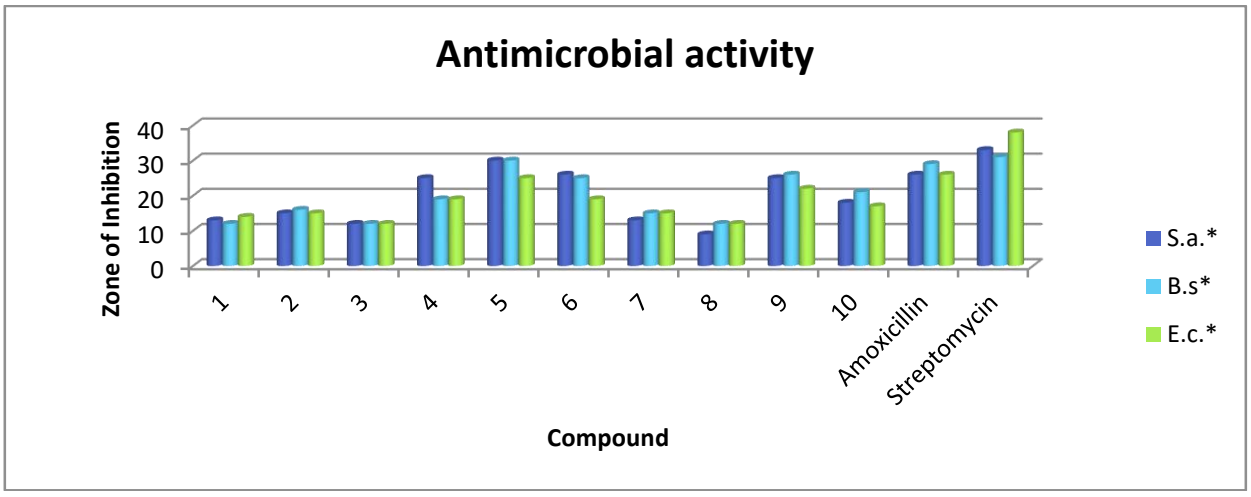


Figure-1: Comparison of zone of inhibition of compounds and standard drugs.

The results revealed that all newly synthesized compounds were exhibited moderate antibacterial activity against both Gram positive and Gram negative bacteria. Compound 4, 5, 6 and 9 were most active against three bacterial strains compared to other synthesized compounds but less potent than the all reference drugs.

Compounds (Concentration 1mmol)	Antifungal activity (mm)	
	Yeast	Mould
	C.t.*	A.n.*
1	9	11
2	11	11
3	11	11
4	**13**	**17**
5	13	15
6	8	11
7	**14**	**16**
8	9	9
9	**15**	**15**
10	10	12
Fluconazole	17	19
DMSO	---	---

Table 4: The zone of inhibition values (mm) of compounds [1-10]: *C.t - *Candida tropicalis**A.n. - *Aspergillus niger*
DMSO – No activity

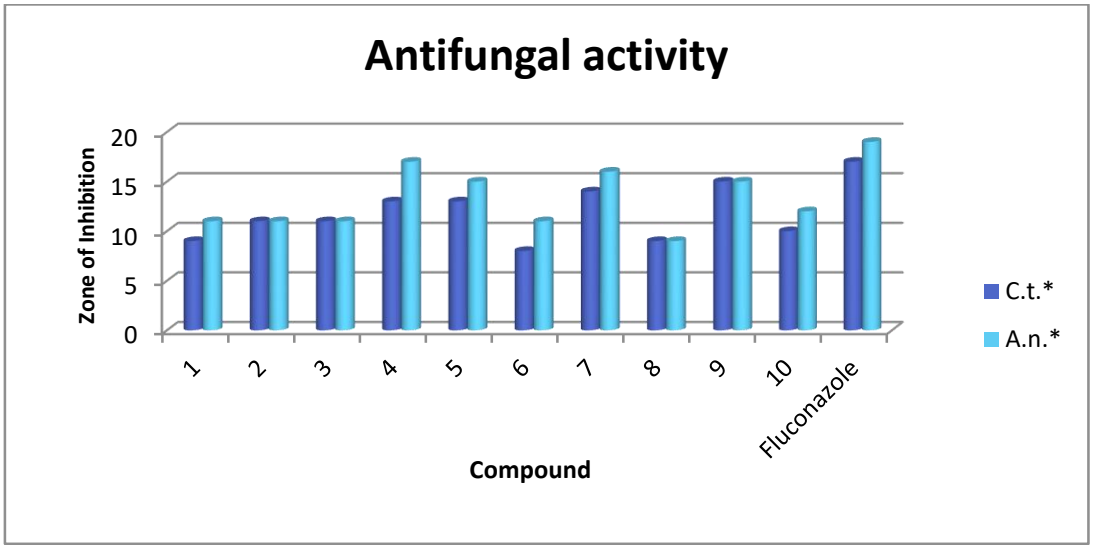


Figure-2: Comparison of zone of inhibition of compounds and reference drugs.

The antifungal screening results (the zone of inhibition), presented in table 4. From the results we recognized that all newly synthesized compounds were exhibited moderate antifungal activity against both yeast and mould. Compound 4, 7 and 9 were most active compounds against both yeast and mould compared to other synthesized compounds but less potent than the reference drug.

The minimum inhibitory concentration:

Micro dilution is used according to a standard protocol described by the NCCLS. Five stains were tested each of the following species: *Escherichia coli, Bacillus substillis, Staphylococcus aureus, Candida tropicalis, Aspergillus niger.*

Compounds	Antibacterial activity (µg/ml)			Antifungal activity (µg/ml)	
	Gram positive		Gram negative	yeast	Mould
	S.a.*	B.s*	E.c.*	C.t.*	A.n.*
1	350	450	400	400	350

2	450	400	450	300	350
3	400	400	450	400	400
4	300	350	250	300	250
5	250	350	350	150	200
6	300	450	400	200	250
7	400	350	250	300	350
8	450	450	450	450	400
9	250	300	250	200	200
10	350	400	300	250	300
Fluconazole	---	---	---	50	25
Amoxicillin	50	50	75	---	---
Streptomycin	25	50	25	---	---

Table-5: Minimum inhibitory concentrations (MIC) values (µg/ml) of the synthesized compounds\
*E.c. – Escherichia coli * C.t - *Candida tropicalis**B.s-*Bacillus substillis* *A.n. – Aspergillus niger *S.a. – Staphylococcus aureus

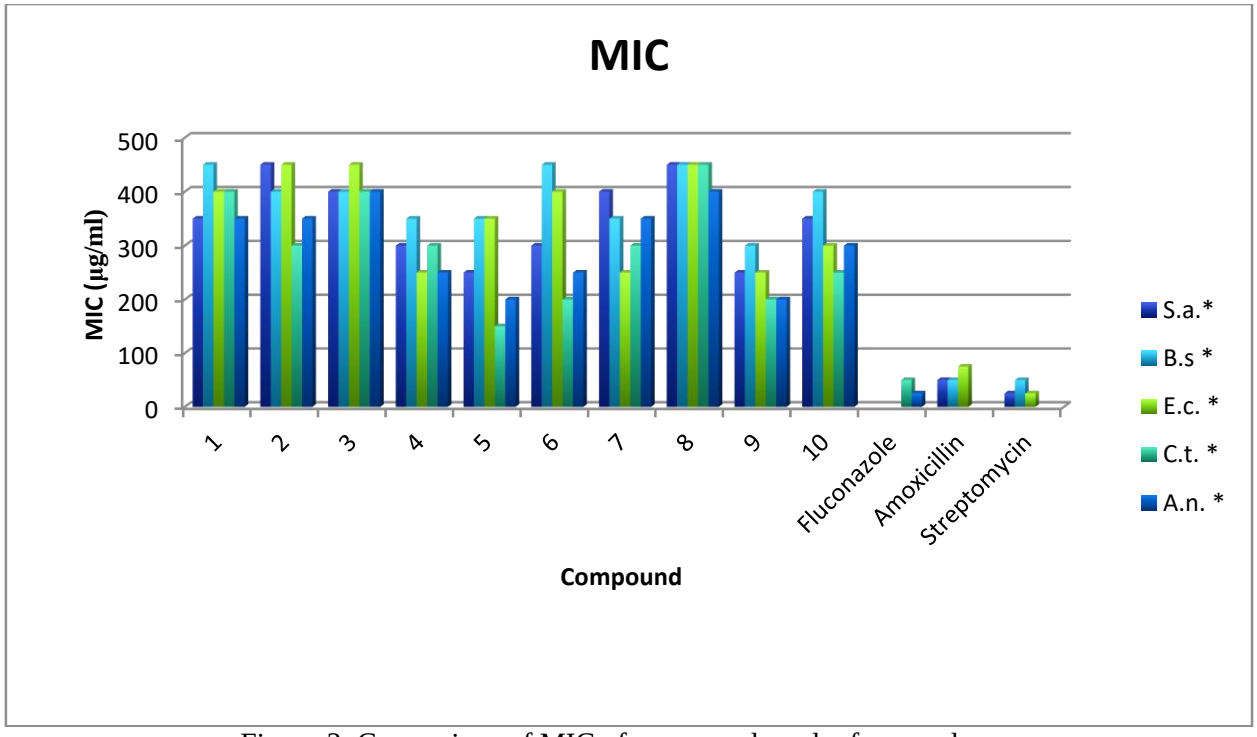


Figure-3: Comparison of MIC of compounds and reference drugs.

Table 5 showed the MIC values of the newly synthesized drugs as well as the standard drugs Fluconazole as antifungal and Amoxicillin & Streptomycin as antibacterial. Compound 4, 7 and 9 is the more active against Gram positive bacteria than the Gram negative bacteria. Compound 4, 5 and 9 are more active against mould than yeast.

4. CONCLUSION:

According to various results of thiazole derivatives against bacterial and fungal species we conclude that compounds no. 4, 5, 6 and 9most active against three bacterial strains and Compound 4, 7 and 9 were most active compounds against both yeast and mould. Among all the compounds compound no. 4 and 9 shows better activity against bacterial as well as fungal species. Compound 4 contain amino fluorine derivatives and compound 9 contain morphiline derivatives both the derivatives are highly electronegative so it gives better activity against all the species.

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